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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/884,901	06/18/2001	Carol H. Miao	UOFW117396	1704

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EXAMINER	
BURKHART, MICHAEL D	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 12/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/884,901	MIAO ET AL.	
	Examiner	Art Unit	
	Michael D. Burkhart	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *32-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *6/18/2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/19/04; 9/19/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Priority

This application, filed 6/18/2001, claims benefit from application 60/212,902, filed 6/20/2000. The application is granted a priority date of 6/20/2000.

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-31, in the reply filed on 7/29/2004 is acknowledged. The traversal is on the ground(s) that the methods of Group II use the vectors of Group I, therefore there is no burdensome search. This is not found persuasive because whereas the respective searches of the claimed vectors and methods may overlap, they are not coextensive. To search the methods would require additional search terms, and, the Groups have been classified in separate classes and subclasses. As a proof-of principle, certain prior art documents anticipating the claimed nucleic acids and vectors (see below) do not disclose methods of treating disease.

The requirement is still deemed proper and is therefore made FINAL.

Claims 32-35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 7/29/2004.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-6 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2-6 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: a structural element of the claimed expression cassette that accounts for the long-term expression limitations (i.e. 100, 300, or 500 days). For example, the expression of cassette of claim 1 placed in a typical plasmid, then transfected into cell culture, would not express a polypeptide for the claimed time periods as the cells would die. The only situations disclosed by applicants and the art where expression would occur for the claimed time periods are transgenic animals and/or recombinant AAV vectors. However, it is unclear whether these elements are included in the claimed invention. Therefore, the metes and bounds of the claimed subject matter are unclear.

Claim 26 recites, in lines 3-4, that the "intron comprises the nucleic acid set forth in SEQ ID NO: 2". However, the specification (see description of Fig. 7A) indicates that SEQ ID NO: 2 is the Factor IX cDNA, which by definition does not comprise any introns, only exons. Thus, it is unclear if the claimed expression cassette contains an intron or contains the Factor IX cDNA. Therefore, the metes and bounds of the claimed subject matter are unclear.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 11 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants claim a nucleic acid expression cassette comprising a hepatic promoter, wherein the hepatic promoter comprises a hepatic nuclear factor binding site consisting of SEQ ID NO: 10. Applicants loosely define a hepatic promoter as any promoter which directs expression in liver cells, then disclose examples of various hepatic promoters, such as the α-1 antitrypsin, HBV, and albumin promoters (page 9, line 22 to page 10, line 2). The only information available for SEQ ID NO: 10 (via the Sequence Listing) is that it is a consensus sequence for a hepatic nuclear factor binding site. Thus, the claims read on a broad genus of promoters consisting of any promoter that directs expression in liver cells and which has SEQ ID NO: 10 inserted (or used to replace a native sequence) anywhere within the promoter sequence. For example, using only the α-1 antitrypsin promoter, (SEQ ID NO: 5, 418 nucleotides) and using only an insertion strategy for SEQ ID NO: 10, 418 different species are possible if SEQ ID NO: 10 were sequentially inserted 3' to every nucleotide in the α-1 antitrypsin promoter. This number of species is doubled if a simple replacement strategy is used sequentially over the length of the α-1 antitrypsin promoter (i.e. the 8 nucleotides of SEQ ID NO: 10 are used to replace 8 nucleotides of SEQ ID NO: 10). Therefore, even in a limited example with a single promoter, the claim embraces over 800 possible species of hepatic promoters.

The written description requirement for a genus may be satisfied by sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant

identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show that applicant was in possession of the claimed invention. In the instant case, applicants only disclose the α-1 antitrypsin promoter and other elements of a nucleic acid expression cassette. Neither applicants nor the prior art disclose hepatic promoters containing SEQ ID NO: 10. Rather, because it is a consensus sequence, hepatic promoters containing sequences similar to SEQ ID NO: 10 are disclosed. For example, SEQ ID NO: 10 is disclosed as TGTAACAG and the α-1 antitrypsin promoter contains (at residues 16-23 of SEQ ID NO: 5) the sequence TGGAACAG, which differs from SEQ ID NO: 10 by a single residue (the underlined G). Thus, there are no teachings that the SEQ ID NO: 10 consensus sequence can actually function as a binding site for a hepatic nuclear factor. Applicants claim hepatic promoters comprising SEQ ID NO: 10 by function only, without a correlation between structure and function. The lack of disclosure and broad genus regarding the claimed hepatic promoters would require the skilled artisan to conclude that the example presented by the applicants is not sufficient to describe the claimed genus.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-9, 12-16, 18, 20-24, 26-31 are rejected under 35 U.S.C. 102(a) as being anticipated by Miao et al (Mol. Ther., June 2000, cited in the IDS of 7/19/2004). A telephone call to the publisher (Elsevier) revealed this document was published on 6/13/2000. The claims recite a nucleic acid expression cassette comprising: an hepatic locus control element (HCR); an hepatic promoter 3' to the HCR; a coding sequence 3' to the promoter; a polyadenylation (poly A) signal 3' to the coding sequence; and an intron 3' to the promoter and 5' to the poly A signal. The above elements are operably linked such that the polypeptide encoded by the coding sequence is expressed. The HCR may hybridize to or consist of SEQ ID NO: 4, or consist of SEQ ID NO: 9. The promoter may be constitutive, hybridize to or consist of SEQ ID NO: 5. The coding sequence may encode a blood clotting polypeptide, which may be Factor IX and consist of SEQ ID NO: 3. The intron may be 3' to the coding sequence, may hybridize to an intron sequence found in a gene encoding the polypeptide sequence, may be a Factor IX intron, and may consist of SEQ ID NO: 1. The poly A signal may hybridize to or consist of SEQ ID NO: 6. Also claimed is a vector comprising the above expression cassette, which may be an episomal vector, which may be a plasmid, or an integrating vector, which may be a viral vector. Claims 2-6 recite intended use limitations wherein the claimed expression cassette directs expression of the polypeptide for 100-500 days. Since these limitations depend upon how the cassette is used (i.e. in a transgenic animal) rather than what it is, these limitations do not limit the structure of the claimed cassette. Hence, any disclosure of the claimed cassette structure is considered anticipatory.

Miao et al teach retroviral and plasmid vectors comprising expression cassettes comprising: the ApoE HCR (SEQ ID NO: 4) or a fragment of the ApoE HCR (SEQ ID NO: 9);

the human α-1 antitrypsin promoter (hAATP, SEQ ID NO: 5); a sequence encoding Factor IX (a clotting factor, SEQ ID NO: 3) which may include the Factor IX Intron A (SEQ ID NO: 1) 3' to the coding sequence; and, the bovine growth hormone poly A signal (bpA, SEQ ID NO: 6). The cassette(s) were placed into pBluescript (episomal plasmids) or retroviral vectors (integrating). See Fig.1 and page 523, second column entitled "Methods" to page 525, first column.

Claims 1-4, 7-9, 17-20, and 27-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Fazio et al (J. Clin. Invest., 1993) as evidenced by Simonet et al (J. Biol. Chem., 1993, cited by applicants) and Dang et al (1995, cited by applicants). The claims are described above, except the intron may be 5' to or within the coding sequence. Fazio et al teach a vector comprising a 3.8 kb fragment from the Apo E/CI/CI'/CII locus ligated 5' to the human ApoE gene (page 1498, first column under "Methods"). The 3.8 kb fragment inherently contains the ApoE HCR as disclosed by Simonet et al, which is the same ApoE HCR used by applicants (i.e. SEQ ID NO: 4). Lines 33-35 on page 14 of the specification disclose that SEQ ID NO: 4 was prepared by PCR from plasmid pLIV7 as taught by Dang et al. A review of Dang et al fails to reveal a plasmid named pLIV7, but does reveal SEQ ID NO: 4 in Fig. 1. This ApoE HCR taught by Dang et al in Fig. 1 was taken from the LE6 construct taught by Simonet et al (see page 22577, second column of Dang et al and Fig. 2 of Simonet et al) which itself is contained within the LE1 construct, the 3.8kb fragment used by Fazio et al. Thus, the 3.8kb fragment taught by Fazio et al inherently contains the same HCR as used by applicants. The human ApoE gene used by Fazio et al inherently comprises a hepatic promoter (it is expressed in the liver), three introns interspersed between four exons, and a poly A signal (see Simonet et al, Figs. 1 and 2). Fazio et

al use the above ApoE vector (a plasmid) to prepare transgenic animals, which by definition requires an integration of the transgenic construct into the genome, and thus, an integrating vector.

Claims 1-4, 7-9, 17-19, and 27-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Simonet et al (J. Clin. Invest., 1994) as evidenced by Simonet et al (J. Biol. Chem., 1993, cited by applicants). The claims are described above. Simonet et al disclose the HE8 vector in Figure 1 (page 1312) which comprises (5'-3'): an HCR; the ApoE promoter, ApoE exon 1, Intron 1, and a partial exon 2; an Il-8 cDNA; and an SV40 poly A signal. The HCR is the same as described above, i.e. from fragment LE6 as described in Fig. 2 of Simonet et al (1993), and thus is the same as SEQ ID NO: 4 as disclosed by applicants (see the section entitled "Constructs" bridging pages 1310 and 1311 of Simonet et al 1994). As stated above, the ApoE promoter is considered an hepatic promoter because it directs expression in liver cells. The ApoE intron is 5' to a coding sequence (ApoE exon 1), 3' to the partial Exon 2, and thus is also within the coding sequence. The HE8 vector (a plasmid) is used to prepare transgenic mice (se abstract and Figs. 1 and 2), which by definition requires an integration of the transgenic construct into the mouse genome, and thus, an integrating vector.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-10 and 12-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Snyder et al (U.S. Patent 6,936,243, effective filing date of 12/2/1996 as evidenced by Simonet et al, 1993 and 1994, as cited above and Nguyen et al (Oncogene, 1996)) in view of Jallat et al (EMBO Journal, 1990) and Kurachi et al (J. Biol. Chem., 1995).

The claims are described above, except that the hepatic promoter may be inducible and the nucleic acid expression cassette may comprise: an HCR that hybridizes to that set forth in SEQ ID NO: 4; a hepatic promoter that hybridizes to the sequence set forth in SEQ ID NO: 5; a coding sequence 3' to the promoter; an intron 5' to the coding sequence and 3' to the promoter; and, a poly A signal 3' to the coding sequence.

Snyder et al teach recombinant AAV vectors for expression of human Factor IX (SEQ ID NO: 3) which may comprise the Apo E HCR-1 or HCR-2 (column 14, lines 10-15). This HCR-1 is the same as SEQ ID NO: 4 for reasons explained in the102 (b) (Fazio et al) rejection above, i.e. both are derived from the same Apo E HCR disclosed by Simonet et al (1993 and 1994, see above). In describing HCR-1, Snyder et al reference Nguyen et al (column 14, lines 12-14).

Nguyen et al describe a vector (page 2117, first column, para. entitled "Transgene preparation") using the ApoE promoter and enhancer from plasmid HE8 as described by Simonet et al (1994). As described above, HE8 contains (5'-3') the ApoE HCR, promoter, Exon 1, Intron 1, and a portion of Exon 2 followed by IL-8 cDNA and a poly A (Fig. 1 of Simonet et al, 1994). Thus, Snyder et al teaches the use of the ApoE HCR and, inherently, teaches the 5'-3' order of the HCR and hepatic promoter of the claimed nucleic acid expression cassette. Snyder et al teach that the hepatic promoter may be hAATP (column 14, lines 15-17), which is SEQ ID NO: 5, and the promoter may be constitutive or regulatable, which includes inducible promoters (column 13, lines 27-40). The vector may comprise a polyadenylation signal, which may be the bovine growth hormone poly A (SEQ ID NO: 6), as detailed in column 18, lines 20-21. The vectors are in the form of plasmids and AAV vectors/genomes (column 18, line 11 to column 19, line 7). Snyder et al teach that the primary use for their vectors is for delivery of genes to the liver in order to treat liver disease, and that one such disease is hemophilia B, caused by a deficiency of Factor IX (column 5, line 12 to column 6, line 47). Snyder et al do not teach the use of a Factor IX intron in the nucleic acid expression cassette, but rather the Factor IX cDNA (column 18, lines 15-20).

Jallat et al teach that deficiency of Factor IX results in hemophilia B, and that inclusion of the full length Intron A or a 1.4 kb fragment of Intron A (SEQ ID NO: 1) of the Factor IX gene increased expression of Factor IX in transgenic mice. See the abstract; first column to second column, second paragraph of page 3295; constructs pTG3960 and pTG3954 in Fig. 1 and Table II; and description of the constructs in the first column, page 3300 under "Materials and methods".

Kurachi et al also teach that deficiency of Factor IX results in hemophilia B, and that a 1.4 kb fragment of Intron I of Factor IX (SEQ ID NO: 1) enhances expression of Factor IX. The use of the terms "Intron I" or "Intron A" to describe the first intron of the Factor IX gene appears interchangeable, as Kurachi et al is based upon Jallat et al, who use the term "Intron A" (see above). See the abstract, first and second columns of page 5276, construct FIXm1 in Fig. 2, and Table II.

The claimed nucleic acid expression cassettes are essentially disclosed in the recombinant AAV vectors of Snyder et al with the exception of the inclusion of an intron. The ordinary skilled artisan, seeking a method to treat hemophilia B by increasing Factor IX expression, would have been motivated to include Intron A or the 1.4kb fragment of Intron A (represented by SEQ ID NO: 1) with the AAV vectors of Snyder et al because Jallat et al and Kurachi et al teach the inclusion of these sequences to increase the expression of Factor IX. It would have been obvious for the skilled artisan to do this because of the known benefit of increasing Factor IX expression in the treatment of hemophilia B, as taught by Snyder et al, Jallat et al, and Kurachi et al. Given the teachings of the cited references and the level of skill of the ordinary skilled artisan at the time of applicants' invention, it must be considered, absent evidence to the contrary, that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael D. Burkhart whose telephone number is (571) 272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michael D. Burkhart
Examiner
Art Unit 1633

Scott D. Priebe

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PRIMARY EXAMINER